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Interleukin-1 beta induces corticotropin-releasing factor-41 release from cultured hypothalamic cells through protein kinase C and cAMP-dependent protein kinase pathways.

Hu SB, Tannahill LA, Lightman SL

Neuroendocrinology Unit, Charing Cross and Westminster Medical School, Charing Cross Hospital, London, UK.

Interleukin-1 beta (IL-1 beta) induces a dose-dependent increase in the release of corticotropin-releasing factor-41 (CRF) from dispersed rat fetal hypothalamic cells in culture. This release of CRF could be inhibited by the protein kinase C inhibitor H-7, and by the protein kinase A inhibitor IP-20. This suggests that both protein kinase C and protein kinase A-dependent pathways are involved in the response of CRF to IL-1 beta. Dexamethasone also blocked the CRF response to IL-1 beta, indicating that activated glucocorticoid receptors can inhibit the response of CRF to IL-1 beta.

PMID: 1517398, UI: 92388406

Revised: January 10, 2000.

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Fibroblast growth factor-2 and TPA enhance prostate-cancer-cell proliferation and activate members of the Ras and PKC signal transduction pathways.

Hrzenjak M, Shain SA

Department of Obstetrics and Gynecology, The University of Texas Health Science Center at San Antonio, 78284-7836, USA.

Rat prostate-cancer-cell stable-transfectants expressing either antisense-fibroblast growth factor (FGF-1) or antisense-FGF-2 transcripts that respectively have either undetectable FGF-1 or profoundly diminished FGF-2 protein content, were used for analyses of FGF-2 and/or 12-O-tetradecanoylphorbol 12-acetate (TPA) modulation of cell proliferation. Antisense-FGF-2 transfectant doubling-time was 2.6-fold greater than that of vector-control transfectants. FGF-2 and TPA respectively caused 2.5- and 3.0-fold reductions in antisense-FGF-2 transfectant doubling-time. Culture of antisense-FGF-2 transfectants in medium containing both FGF-2 and TPA further reduced their doubling time; however, this effect was not statistically different from that achieved by TPA treatment alone. Antisense-FGF-1 transfectant doubling-time was 2.2-fold greater than that of vector-control transfectants and was reduced 2.0- or 2.3-fold, respectively, when these cells were cultured in medium containing FGF-2 or TPA. In contrast to the results for antisense-FGF-2 transfectants, culture of antisense-FGF-1 transfectants in medium containing both FGF-2 and TPA caused a 2.6-fold reduction in transfectant doubling-time that was significantly greater than that caused by independent treatment with either FGF-2 or TPA. FGF-2 promoted rapid activation of rat prostate-cancer-cell PKCalpha and PKCepsilon, as assessed by isozyme translocation from the soluble to particulate cell fraction, and only moderately altered PKCdelta distribution. By contrast, TPA promoted rapid activation of all three PKC isozymes. Both the TPA- and FGF-2-mediated PKC activation were prolonged and possibly involved cyclic redistribution of isozymes between soluble and particulate cell fractions. FGF-2 also caused rapid phosphorylation of prostate-cancer-cell Shc, the adapter protein that mediates FGF-receptor-modulated ras signaling. The results of these studies

indicate that FGF-2 and TPA independently and conjointly modulate rat prostate-cancer-cell antisense-transfectant doubling time and suggest that effector modulation of rat prostate-cancer-cell proliferation is achieved by processes involving PKC and/or ras mediated signaling.

PMID: 9633822, UI: 98295579

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Effects of PKC activation and receptor desensitization on neurosteroid modulation of GABA(A) receptors.

Leidenheimer NJ, Chapell R

Department of Pharmacology and Therapeutics, Louisiana State University Medical Center, Shreveport 71130-3932, USA. nleide@lsumc.edu

The effect of calcium-phospholipid-dependent protein kinase (PKC) activation on neurosteroid modulation of the GABA(A) receptor was examined in Xenopus oocytes expressing human recombinant alpha1beta2gamma2L GABA(A) receptors. GABA-gated chloride currents were measured using the two-electrode voltage-clamp technique. The peak amplitude of GABA-gated chloride currents was reduced by the PKC activator phorbol 12-myristate 13-acetate (PMA), but not by the inactive analog phorbol 12-mono-myristate (PMM). This effect of PMA was inhibited by the protein kinase inhibitor staurosporine. To investigate whether the activation of PKC could alter neurosteroid modulation of the GABA(A) receptor, the effect of PMA was studied on the positive allosteric modulatory steroid 3alpha,21-dihydroxy-5alpha-pregnan-20-one (THDOC) and the negative modulatory neurosteroid pregnenolone sulfate (PS). THDOC potentiation of GABA-gated chloride currents was found to be increased by approximately 120% following PMA treatment, while PS inhibition was not affected. The increase in THDOC potentiation by PMA was blocked by staurosporine. No change in THDOC potentiation was observed following PMM treatment. The enhancement of THDOC potentiation following PMA treatment was not due to a shift in the GABA EC50. In addition to inhibiting the peak amplitude of the GABA response, PMA treatment resulted in non-desensitizing GABA responses. Similarly, GABA responses of receptors which had been desensitized with prolonged GABA application also showed a reduction in peak amplitude and reduced desensitization. THDOC potentiation of desensitized receptors was enhanced approximately 70% with respect to non-desensitized receptors. The present results demonstrate that protein phosphorylation and receptor desensitization alter modulation of the GABA(A) receptor complex by some neurosteroids.

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